



Title	Effect of High Tibial Osteotomy on the Distribution of Subchondral Bone Density Across the Proximal Tibial Articular Surface of the Knee With Medial Compartment Osteoarthritis
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25

30 **Abstract**

31 **Background:** The effect of high tibial osteotomy (HTO) on the stress distribution across
32 the knee joint is not completely understood. The subchondral bone density is considered
33 to reflect the pattern of stress distribution across a joint surface.

34 **Purpose:** To assess the distribution of subchondral bone density across the proximal tibia
35 in nonarthritic knees and in the knees of patients with osteoarthritis before and after HTO.

36 **Methods:** We retrospectively collected radiographic and computed tomography (CT)
37 data from 16 nonarthritic subjects (control group) and 17 patients with OA (OA group).
38 Data from the OA group were collected before and 1.5 year after HTO. The subchondral
39 bone density of the proximal tibia was assessed with CT–osteodensitometry. The
40 locations and percentages represented by high-density areas on the articular surface were
41 quantitatively analyzed.

42 **Results:** The ratio of the high-density area of the medial compartment to the total high-
43 density area (medial ratio) was significantly higher in preoperative OA patients (mean,
44 80.1%) than in control subjects (61.3%) ($p < 0.001$). After HTO, the medial ratio
45 decreased significantly (to 75.1%, $p = 0.035$, in comparison with preoperative values) and
46 was significantly correlated with the hip–knee–ankle angle (HKA) in both the control
47 ($r = -0.551$, $p = 0.033$) and OA groups ($r = -0.528$, $p = 0.043$). The change in medial

48 ratio after HTO was significantly correlated with the change in HKA ($r = 0.587$,
49 $p = 0.035$). In the medial compartment, the high-density area in most lateral areas of four
50 divided subregions increased after HTO, but that of the other medial three subregions
51 decreased.

52 **Conclusions:** In this exploratory study, HTO shifted the high-density area of the medial
53 compartment of the proximal tibial articular surface toward the lateral compartment. In
54 contrast, the high-density area of the most lateral region of the medial compartment
55 decreased after HTO. This change in subchondral bone density may result from the
56 change in stress distribution.

57 **Clinical relevance:** Assuming that the subchondral bone density is a surrogate for stress,
58 HTO shifts the stress from the medial compartment to the lateral compartment but
59 increases the stress on the most lateral region of the medial compartment.

60 **Key terms:** high tibial osteotomy, knee, osteoarthritis, stress distribution, CT–
61 osteoabsorptiometry, alignment

62 **What is known about the subject:** HTO has been suggested to decrease the stress on
63 the medial compartment of the knee joint. However, the effect of HTO on the stress
64 distribution across the knee joint is not completely understood.

65 **What this study adds to existing knowledge:** HTO decreases the stress on the medial

66 compartment of the proximal tibial articular surface and shifts the distribution of stress
67 toward the lateral compartment. Moreover, the stress on the medial compartment does not
68 decrease across the whole area after HTO and actually increases at the most lateral region.

69 **Introduction**

70 Biomechanical risk factors for knee osteoarthritis (OA), such as obesity, trauma,
71 malalignment, meniscal deficiency, and muscle weakness, increase the mechanical stress
72 across the knee joint. Some of these factors are believed to be important and potentially
73 modifiable factors that determine the site⁴⁵ and severity⁴⁵ of knee OA. Identifying the
74 distribution of mechanical stress across the knee joint would thus contribute to the
75 prediction and management of OA progression.

76 Malalignment of the lower limbs is a strong risk factor for progression of knee
77 OA, and one of the few risk factors that can be modified *a posteriori*. Valgus high tibial
78 osteotomy (HTO) is an established surgical procedure that can be used to treat medial
79 knee OA. HTO reduces loading of the medial compartment and, thereby, slows disease
80 progression. Because it extends the healthy life expectancy of the knee, HTO is widely
81 used as a treatment option for medial OA with varus alignment.^{3, 10, 16} The relationships
82 among leg alignment, medial compartment loading, and change in medial compartment
83 loading after HTO have been examined in a cadaveric study,¹ finite element analyses,^{36,}
84 ⁵² and three-dimensional (3-D) gait analyses by assessing the knee adduction moment
85 (KAM)^{7, 15, 29}; however, how the distribution of the actual stress within each compartment
86 changes after HTO remains unclear.

87 The distribution of the subchondral bone mineral density is thought to be
88 correlated with the distribution of stress over the joint surface; because of the varying
89 degrees of mineralization over the surface of a joint, a materialized field of stress is
90 observed.⁴² Computed tomography (CT)–osteosorptiometry was developed by Müller-
91 Gerbl et al. as an analytical method to assess the long-term stress distribution over
92 individual joints in living participants by measuring the subchondral bone mineral
93 density.^{31, 32} This method generates a precise map of the distribution pattern of
94 subchondral bone density over various articular surfaces. Our previous studies involving
95 this method have evaluated the distribution of subchondral bone density to assess the
96 pattern of stress distribution at the wrist, elbow,³⁴ and the glenohumeral,^{12, 46}
97 patellofemoral,³⁷ and ankle joints⁴¹ in normal people, those with pathological conditions,
98 and athletes. The distribution pattern of subchondral bone density over the knee joint has
99 been suggested to be related to the presence of knee OA^{19, 39}; however, it is unclear
100 whether leg alignment affects the distribution of bone density. Furthermore, whether or
101 how the distribution pattern of subchondral bone density changes on the articular surface
102 across the knee joint after HTO is yet to be elucidated.

103 Using CT–osteosorptiometry, a precise map of the subchondral bone density
104 distribution across the knee joint could provide insight into the stress distribution across

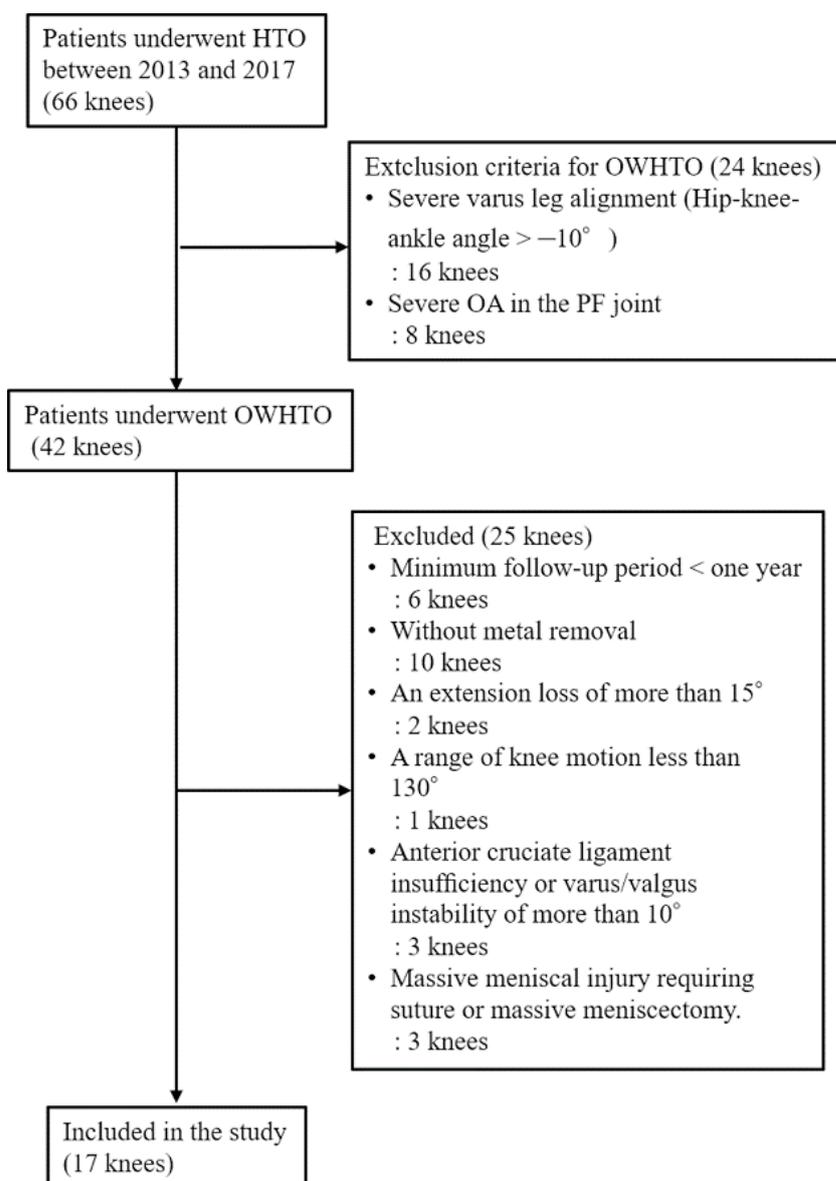
105 the articular surface of the knee joint with and without OA and the change in the stress
106 distribution after HTO. Thus, we hypothesize that valgus HTO leads to a reduction in the
107 *in vivo* subchondral bone density on the medial compartment of the femorotibial joint in
108 the case of varus OA of the knee. The aims of this exploratory study were: (1) to evaluate
109 the distribution pattern of subchondral bone density across the proximal tibia in patients
110 with and without OA, (2) to assess changes in the pattern of bone density distribution in
111 patients with OA before and after HTO, and (3) to clarify the correlation of leg alignment
112 with changes in bone density distribution.

113 **Methods**

114 **Study design**

115 This study was approved by the institutional review board of Hokkaido
116 university hospital (017-0163). We retrospectively recruited all patients who underwent
117 HTO for medial compartment OA between April 2013 and March 2017 at our institution.
118 All operations were performed by a senior orthopedic surgeon (EK) who had over 20
119 years of experience in performing knee surgery. The OA group included patients who
120 underwent medial open wedge HTO (OWHTO) for medial compartment OA. Indications
121 for OWHTO in our hospital were: (1) moderate varus leg alignment (HKA of $>-10^\circ$) and
122 (2) absence of OA in the patellofemoral joint (Kellgren–Lawrence [KL] grade²¹ \geq II) or

123 anterior knee pain. Exclusion criteria were: (1) lateral knee OA (KL grade \geq II) or lateral
124 knee pain, (2) not completing a follow-up period of at least 1 year, (3) having no metal
125 removal after HTO, (4) loss of $>15^\circ$ of knee extension before and after HTO, (5) knee
126 range of motion of $<130^\circ$ before and after HTO, (6) anterior cruciate ligament
127 insufficiency or varus/valgus instability of $>10^\circ$, (7) medial meniscal injury \geq grade 3
128 (Lotysch and Mink's magnetic resonance imaging [MRI] grading system^{5, 30}) or any tear
129 of the medial meniscus for which partial meniscectomy or other repair was performed,
130 and (8) any lateral meniscal injury. Finally, we evaluated 17 knees in 16 patients in the
131 OA group (Figure 1).



132

133 **Figure 1.** Flowchart of study enrollment

134 Abbreviations: HTO, high tibial osteotomy; OA, osteoarthritis; OWHTO, open wedge
135 HTO.

136

137 We also collected the data of 16 patients who underwent simultaneous
138 radiographical and CT examinations of bilateral knees for comparison of ipsilateral knee
139 trauma between April 2013 and March 2017 as control subjects. The uninjured
140 contralateral knee was used as control. Inclusion criteria for the control group were (1)

141 knee OA (KL grade ≤ 1) in the contralateral knee and (2) patients aged 15–30 years at the
142 time of CT scanning. Exclusion criteria for the control group were (1) current pain in the
143 contralateral knee and (2) previous surgery in the contralateral knee.

144 Postoperative clinical and radiological evaluations were performed around
145 1.5 years (mean: 17.4 months, range: 14–25 months) after OWHTO and immediately
146 after removal of the locking plate.

147 **Preoperative planning**

148 Miniaci's method was used for preoperative planning as previously reported.^{33,}
149 ^{43, 49} To calculate an appropriate angle of the medial opening wedge, a long line, [A], was
150 drawn from the center of the femoral head through the 65% lateral from the medial edge
151 of the tibial plateau on the lateral tibial plateau. Another line, [B], was then drawn from
152 the hinge point [P] to the center of the talar dome, and its length was measured. An arc,
153 [C], the center and the radius of which are the hinge point P and line B, respectively, was
154 then drawn so that the arc crossed line A. A line, [D], was then drawn from the hinge point
155 to the crossing point between line A and the arc C. The angle formed between lines B and
156 D provides the medial opening angle, which is identical to the correction angle of the
157 lower limb alignment.

158 **Surgical technique**

159 Surgery was performed as previously described.^{40, 43, 49} The proximal tibia was

160 exposed through a 7-cm medial longitudinal incision. Further, after the complete release
161 of the distal attachment of the superficial medial collateral ligament, three pairs of
162 Kirshner wires (K-wires) were inserted into the tibia so that each inserted K-wire
163 precisely reached the proximal tibiofibular joint using the parallel guide. We then
164 performed a biplanar osteotomy of the tibia, after which the oblique osteotomy site was
165 gradually opened—according to the preoperative planning angle—using a specially-
166 designed spreader (Olympus Terumo Biomaterials, Tokyo, Japan). Under fluoroscopic
167 control, we set a long straight metal rod to connect the center of femoral head and ankle,
168 then measured the transection point of the rod through the tibial plateau. This was
169 expressed as a percentage of the tibial width from medial-to-lateral. We confirmed the
170 transection point of 65%.¹¹ Two wedged beta-tricalcium phosphate spacers (Osferion 60;
171 Olympus Terumo Biomaterials) were implanted into the anterior part and posterior part
172 of the opening space in a parallel fashion. We fixed the tibia with a locking plate (Tomofix;
173 DePuy Synthes, Raynham, MA, USA, or TriS Medial HTO plate system; Olympus
174 Terumo Biomaterials) by inserting eight locking screws.

175 Each patient underwent an additional procedure approximately 1 year (mean:
176 13.4 months, range: 12–15 months) after the initial surgery to remove the locking plate.
177 Arthroscopic evaluation was performed simultaneously to evaluate the status of the

178 meniscus after HTO.

179

180 **Evaluation criteria**

181 *Clinical evaluation*

182 Patients were evaluated according to the Japanese Orthopaedic Association
183 (JOA) knee scoring system (total, 100 points),^{4, 50} which is the standard knee subjective
184 score used in clinics in Japan. The JOA knee score consists of four categories: “pain on
185 walking” (0–30 points), “pain on ascending and descending stairs” (0–25 points), “range
186 of motion” (0–35 points), and “joint effusion” (0–10 points).

187 *Meniscus status evaluation*

188 To compare meniscus status before and after HTO, an examiner (KI) evaluated
189 the arthroscopic images at HTO as well as at plate removal and MRI images before HTO
190 as well as after plate removal according to the Lotysch and Mink’s MRI grading system.³⁰
191 The change in meniscal status after HTO was graded according to three categories:
192 deterioration, no change, and improvement.

193 *Radiological evaluations*

194 Standing anteroposterior and lateral radiographs of the knee and full-length
195 anteroposterior radiographs of the whole lower limb with the knee in full extension were

196 acquired. The radiological stage of OA was assessed according to the KL grading
197 system.²¹ We measured HKA on anteroposterior radiographs of the whole lower limb
198 taken with a long cassette in the one-leg standing position. We also calculated the
199 percentage of mechanical axis (%MA) as follows: A line was drawn between the center
200 of the femoral head and the center of the tibial plafond; the medial edge of the tibia plateau
201 was defined as 0% and the lateral edge as 100%, and the %MA was the point at which
202 the line passed across the tibial plateau.^{8, 20, 35, 38, 51} The posterior tibial slope (PTS) was
203 measured as the angle between a line perpendicular to the mid-diaphysis of the tibia and
204 the posterior inclination of the medial tibial plateau on the lateral view.

205

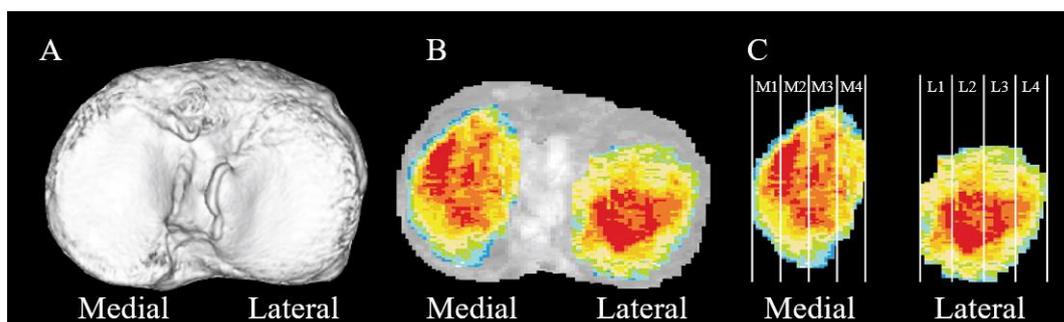
206 *Computed tomography–osteodensitometry*

207 A high-resolution helical CT scanner (Aquilion One/ViSION Edition; Toshiba
208 Medical Systems, Japan) was used to acquire axial images of the knee. Patients rested in
209 a supine position with their knees extended during imaging. Slice thickness and interval
210 were set at 0.5 mm. Acquired CT data were transferred to a personal computer. Sagittal
211 and coronal slices at 1.0-mm intervals and 3-D bone models were generated from axial
212 CT data with the use of commercial software (Ziocube®; Ziosoft, Inc., Tokyo, Japan).
213 We determined the sagittal and coronal axes by reference to the epicondylar axis of the

214 distal femoral condyle at the axial slice. By reference to sagittal and coronal CT images
215 and a 3-D CT image of the articular surface of the proximal tibia, an outline of the medial
216 and lateral compartment of proximal tibial articular surface was manually selected to
217 include the entire subchondral bone layer of the articular surface in all slices.¹² Then the
218 subchondral bone density of each generated sagittal slice was analyzed with our
219 noncommercial software (OsteoDens 4.0) developed at our institution.^{12, 17, 37, 41, 46} The
220 maximum increment point in Hounsfield units from the joint surface as the starting point
221 of the region of interest, and the maximum point in Hounsfield units was selected
222 automatically in the 2.5-mm region of interest from the starting point (Supplementary
223 file). We determined the radiodensity of the identified subchondral bone region at each
224 coordinate point at 1-mm intervals. Then, a two-dimensional image that mapped the
225 distribution of subchondral bone density was obtained by stacking sagittal slices (Figure
226 2A, 2B). The differences between the maximum and minimum values in Hounsfield units
227 on the mapping images were divided into nine grades, and a surface mapping image was
228 generated through the use of these grades to produce a color scale, in which red and violet
229 indicated the greatest and lowest bone densities, respectively. Selected areas of the medial
230 and lateral plateaus included the cortical bone or bony spur at the periphery of the articular
231 surface because it was impossible to exclude the cortical bone or bony spur using the

232 software. However, these features were carefully removed manually from the target area
233 of analysis in subsequent quantitative analysis.¹²

234 Quantitative analysis of the obtained mapping data focused on the location of the
235 high-density area (HDA) of the articular surface. The HDA was defined as the region
236 containing the coordinate points representing the top 20% of Hounsfield unit values out
237 of the total area of the medial and lateral compartments. The medial ratio was calculated
238 as the ratio of the HDA of the medial compartment to the total HDA of both compartments.
239 The medial compartment of the proximal tibia was divided into four subregions of equal
240 width in the coronal direction, denoted M1 to M4 from the medial-to-lateral sides. The
241 lateral compartment was divided equivalently, denoted L1 to L4 from the medial-to-
242 lateral sides (Figure 2C). The percentage of each subregion represented by the HDA was
243 calculated (%HDA).



244
245 **Figure 2.** Identification of the subchondral bone regions of the proximal tibia using a
246 customized software. (A, B) The subchondral bone density of the selected region was
247 automatically measured at each coordinate point in each 1.0-mm sagittal slice. (C) Images
248 of the areas used for quantitative analysis of the bone density mapping data for the medial
249 and lateral compartments of the proximal tibia.

250 Definitions: M1–M4, subregions of the medial compartment of the proximal tibia,
251 divided equally from the medial side to the lateral side; L1–L4, subregions of the lateral
252 compartment, divided equally from the medial side to the lateral side.

253

254 **Statistical analysis**

255 Statistical analyses were performed using JMP Pro 14.0 (SAS Institute Inc., Cary,
256 NC, USA). The significance level was set at $p = 0.05$. Means and 95% confidence
257 intervals (CIs) for the changes after surgery in patients with OA were calculated. We
258 compared controls and patients with OA before and after surgery by using Student's *t* test,
259 and we compared the patients with OA before and after surgery by using a paired *t* test.
260 Pearson's correlation was used to evaluate the relationship between medial ratio and other
261 factors (age, body mass index [BMI], HKA, %MA, and PTS) to compare controls with
262 preoperative patients. In addition, we compared changes from preoperative to
263 postoperative values (denoted by "Δ") of the medial ratio and other variables using
264 Pearson's correlation. These factors were selected because they are believed to influence
265 the distribution of subchondral bone density^{19, 45, 47} or the biomechanics of the knee
266 joint.⁴⁴

267 The reproducibility of data was evaluated using our noncommercial software
268 (OsteoDens 4.0). Intra- and interobserver reliability were assessed on three randomly
269 selected knees from the control group and each OA group. Two observers (KI and SM)

270 independently measured %HDA in these six knees; a total of 48 subregions were
271 measured twice in a blinded manner at 1 month intervals. The intraclass correlation
272 coefficients for intraobserver reliability were 0.922 (KI) and 0.913 (SM), respectively,
273 and the intraclass correlation coefficient for interobserver reproducibility was 0.917.

274

275 **Results**

276 Age, BMI, HKA, and %MA were significantly different between the control and
277 preoperative OA groups ($P < .001$, $P = .026$, $P < .001$, and $P < .001$, respectively; Table
278 1). The medial ratio was 31% higher in the preoperative OA group than in the control
279 group ($P < .001$).

280 After HTO, JOA score improved by 33% ($P < .001$). The sum of “pain on
281 walking” and “pain on ascending and descending stairs” subcategory scores improved by
282 56% ($P < .001$). Significant differences in HKA, %MA, and PTS between the
283 preoperative and postoperative OA groups ($P < .001$, $P < .001$, and $P = .019$, respectively).
284 The medial ratio decreased by 6% after HTO, respectively ($P = .035$; Table 1).

285 In the comparison between the patients with OA after surgery and the controls,
286 leg alignment was significantly more valgus in the patients (5.0 degrees valgus in HKA)
287 compared with the controls (1.5 degrees varus; $P < .001$). The medial ratio was 21%

288 higher in the patients than that in the controls ($P = .008$).

289 Table 1. Patient characteristics, OA grade, leg alignment, clinical outcomes, and medial

290 ratio^a

Characteristic	Controls (n = 16)	Patients with OA (n = 17)		Comparison: preop with control	Comparison: preop with postop		Comparison : postop with control
		Preoperative	Postoperative	<i>P</i> value	Mean change	<i>P</i> valu e	<i>P</i> value
Age, years	20.8 (18.1– 23.4)	58.9 (54.8– 63.0)	n/a	<.001	n/a	n/a	n/a
Male:female ratio	8:8	6:11	n/a	.393	n/a	n/a	n/a
BMI, kg/m ²	24.0 (21.8– 26.2)	27.0 (25.1– 28.9)	n/a	.026	n/a	n/a	n/a
KL grades (III and IV)	n/a	16:1	16:1	n/a	n/a	.99	n/a
HKA, degrees	–1.5 (–3.4– 0.4)	–6.1 (–8.0– –4.2)	5.0 (4.1– 5.8)	<.001	9.9 (7.6– 12.2)	<.00 1	<.001
%MA, %	43.8 (37.3– 50.3)	22.8 (14.9– 30.7)	68.8 (65.3– 72.3)	<.001	45.4 (36.7– 54.0)	<.00 1	<.001
PTS, degrees	9.9 (8.2– 11.6)	11.5 (9.7– 13.7)	13.1 (10.8– 15.4)	.191	1.6 (0.3– 2.8)	.019	.025
JOA knee score, points							
Total	n/a	68.8 (61.3– 76.2)	91.6 (86.6– 96.5)	n/a	22.7 (17.3– 28.3)	<.00 1	n/a

Pain on walking	n/a	19.6 (17.2–21.9)	29.1 (27.7–30.5)	n/a	9.6 (6.8–12.3)	<.001	n/a
Pain on ascending and descending stairs	n/a	13.6 (11.0–16.3)	22.7 (21.0–24.5)	n/a	9.1 (6.5–11.6)	<.001	n/a
Range of motion	n/a	28.6 (26.5–30.8)	30.9 (28.4–33.4)	n/a	2.3 (0.5–4.0)	.02	n/a
Joint effusion	n/a	6.8 (4.6–9.1)	8.3 (7.1–10.2)	n/a	1.8 (0.1–3.5)	.04	n/a
Medial ratio, ^b %	61.3 (55.7–66.9)	80.1 (72.3–85.6)	75.1 (67.8–83.5)	<.001	4.4 (0.6–8.1)	.035	.008

291 ^aData are reported as means (95% confidence intervals) or ratios.

292 ^bMedial ratio: The ratio of high-density area (HDA) of the medial compartment in relation
293 to the total HDA of both compartments. HDA: 20% highest area in Hounsfield unit values
294 out of the sum of the medial and lateral compartments. Varus alignment was a negative
295 value of HKA, and valgus alignment was a positive value.

296 n/a, not applicable. OA, osteoarthritis. BMI, Body mass index. KL, Kellgren–Lawrence.
297 HKA, Hip–knee–ankle angle. %MA, Percentage of mechanical axis. PTS, Posterior tibial
298 slope. JOA, Japanese Orthopedic Association (knee score: total, 100 points). Preop:
299 before HTO. Postop: 1 year after HTO.

300 In arthroscopic evaluation after HTO, meniscal status was graded “no change”
301 in both medial and lateral compartments in all cases. However, Lotysch and Mink’s MRI
302 grading of meniscal status was unchanged in both medial and lateral compartments after
303 HTO.

304 Of the parameters that differed significantly between the control and
305 preoperative OA groups, age, HKA, and %MA were found to be significantly correlated
306 with the medial ratio (Table 2). Only HKA was found to be significantly correlated with

307 the medial ratio in both the control and OA groups (Figure 3).

308 Table 2. Statistical analysis: Pearson correlation (r) between medial ratio and
309 demographic data in controls and patients with osteoarthritis^a

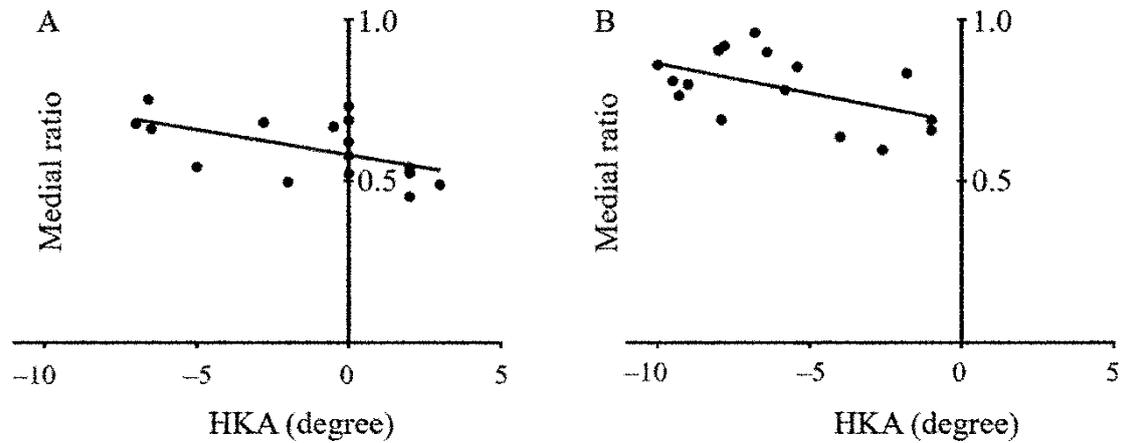
Characteristic	Controls		Patients	
	r	<i>P</i> value	r	<i>P</i> value
Age	0.122	.670	0.671	.009
BMI	-0.144	.609	-0.077	.785
HKA	-0.551	.033	-0.528	.043
%MA	-0.558	.031	-0.432	.108
PTS	-0.126	.654	-0.217	.438

310 ^aMedial ratio: The ratio of high-density area (HDA) of the medial compartment relative
311 to the total HDA of both compartments. HDA: 20% highest area in Hounsfield unit values
312 out of the sum of the medial and lateral compartments.

313 BMI, Body mass index. HKA, Hip-knee-ankle angle. %MA, Percentage of mechanical
314 axis. PTS, Posterior tibial slope.

315

316 **Figure 3.** Relationship between hip-knee-ankle angle (HKA) and medial ratio. (A)
317 Control group: Pearson correlation analysis showing a significant negative correlation
318 between HKA and medial ratio (Pearson $r = -0.551$; $P < 0.033$). (B) OA group: Pearson
319 correlation analysis showing a significant negative correlation between HKA and medial
320 ratio (Pearson $r = -0.528$; $P < 0.043$). Medial ratio: The ratio of high-density area (HDA)
321 of the medial compartment in relation to the total HDA of both compartments. HDA: 20%
322 highest area in Hounsfield units values out of the sum of the medial and lateral
323 compartments.



324

325 Of the patients' characteristics, including age, BMI, sex, and JOA knee score,
 326 none showed a significant correlation with Δ medial ratio. In contrast, of the parameters
 327 that were changed after HTO, only Δ HKA was significantly correlated with the Δ medial
 328 ratio ($P = .035$; Table 3). In addition, there was no significant correlation between Δ HKA
 329 and functional knee score.

330 Table 3. Statistical analysis: Pearson correlation coefficients and partial correlation
 331 coefficients between Δ medial ratio and demographic data in patients with osteoarthritis
 332 before and after HTO^a

Characteristic	Correlation coefficient	<i>P</i> value	Partial correlation coefficient
Pre-HTO HKA	-0.338	.259	-0.431
Pre-HTO PTS	0.0002	.999	0.151
Post-HTO HKA	0.432	.140	0.415
Post-HTO PTS	0.009	.999	0.031
Δ HKA	0.587	.035	0.539
Δ PTS	0.018	.930	0.151

333 ^a Medial ratio: The ratio of high-density area (HDA) of the medial compartment in
 334 relation to the total HDA of both compartments.

335 HDA: 20% highest area in Hounsfield unit values out of the sum of the medial and lateral
 336 compartments. HTO, High tibial osteotomy. HKA, Hip-knee-ankle angle. PTS, Posterior

337 tibial slope. Post-HTO refers to 1 year after HTO. Δ : the value of the change before and
 338 after HTO.

339 Subregional %HDA analysis revealed %HDA of the M2 and M3 regions to be
 340 significantly higher among patients with OA than controls ($P = .011$ and $P < .001$,
 341 respectively). The %HDA of all four subregions of the lateral compartment was
 342 significantly lower in patients with OA than controls (for M1, $P < .001$; for M2, $P = .013$;
 343 for M3, $P = .005$; and for M4, $P = .005$; Table 4). After HTO, the %HDA of M2 and M3
 344 decreased by 23% ($P = .009$) and 20% ($P = .017$), respectively. whereas that of M4
 345 increased by 19% ($P = .014$). In the lateral compartment, the %HDA of L2 and L3
 346 increased by 52% ($P = .026$) and 74% ($P = .006$).

347 Table 4. Subregional analysis of %HDA^a

Subregion	Controls	Patients with OA		<i>P</i> value	
		Preoperative values	Postoperative values	Comparison: Preop with control	Preop–postop change
M1	6.2 (4.6–7.9)	9.5 (6.5–12.6)	7.0 (3.9–10.2)	.051	.112
M2	18.9 (16.4–21.3)	23.4 (20.8–26.0)	18.1 (13.8–22.5)	.011	.009
M3	21.6 (19.8–23.3)	29.0 (26.5–31.6)	23.2 (18.5–28.0)	<.001	.017
M4	16.1 (13.0–19.1)	18.1 (15.1–21.0)	21.6 (18.3–24.9)	.323	.014
L1	12.1 (9.9–14.3)	5.4 (3.5–7.3)	8.1 (4.0–12.1)	<.001	.132
L2	13.5 (11.4–15.6)	9.1 (6.3–12.0)	13.8 (9.4–18.3)	.013	.026
L3	9.0 (6.6–11.4)	4.2 (1.8–6.6)	7.3 (3.7–10.9)	.005	.006
L4	2.7 (1.2–4.2)	0.5 (0.1–0.8)	1.6 (0.2–3.0)	.005	.095

348 ^aData are reported as means (95% confidence intervals).

349 HDA: 20% Highest area in Hounsfield unit values out of the sum of the medial and lateral
350 compartments. %HDA: The percentage of the HDA in each subregion. OA, osteoarthritis.
351 HTO, High tibial osteotomy. Preop: before HTO. Postop: 1 year after HTO. M1–M4:
352 Subregions of the medial compartment of the proximal tibia, divided equally from the
353 medial side to the lateral side. L1–L4: Subregions of the lateral compartment, divided
354 equally from the medial side to the lateral side.

355

356 **Discussion**

357 In this study, we demonstrated that the medial ratio, defined as the ratio of the
358 medial HDA to the total HDA of the proximal tibia, was increased among patients with
359 OA and varus deformity but decreased significantly after valgus HTO. Furthermore, we
360 discovered that leg alignment was significantly correlated to medial ratio in healthy
361 individuals as well as patients with OA and that the degree of correction of alignment
362 after HTO was correlated to the change in medial ratio.

363 According to the results of previous studies involving dual-energy X-ray
364 absorptiometry (DEXA), leg alignment was correlated with bone mineral density (BMD)
365 of the proximal tibia^{2, 25, 47} as well as with the decrease in BMD of the medial
366 compartment after HTO.^{2, 25} These findings are similar to the results of our study.
367 However, DEXA is used to evaluate BMD of the periarticular bone but does not
368 distinguish the subchondral bone plate from trabecular bone of the articular surface or
369 from bone spurs or cortical bone. In addition, according to the results of one experimental

370 study, BMD of subchondral bone and trabecular bone changed differently over time,⁶
371 which suggests the difficulty of evaluating the change in the BMD of subchondral bone
372 precisely with DEXA. In contrast, in CT–osteosorptiometry, bone spurs can be hidden
373 in the region of interest so that the focus is on the subchondral bone plate of the articular
374 surface. This was believed to be an advantage in our study.

375 Previous studies involving CT–osteosorptiometry have indicated that the
376 distribution pattern of subchondral bone density reflects the distribution of the resultant
377 stresses acting on a joint surface under actual loading conditions.^{12, 17, 18, 31, 32, 34, 37, 41, 46}
378 We found the medial ratio to be higher in OA patients than healthy individuals, decreasing
379 after HTO in the former. Moreover, the JOA knee scores improved, particularly in the
380 pain subcategories, after HTO. These results indicated that HTO reduces the stress
381 distribution pattern across the medial compartment of the proximal tibial articular surface.

382 The correlation between Δ HKA and Δ medial ratio was weak ($r = 0.587$), which
383 indicates that the change in leg alignment explained the small variance (~35%) in the
384 Δ medial ratio. Other factors not evaluated in this study, including physical characteristics
385 (e.g., muscle strength, pelvic width), kinetics (i.e., dynamic alignment), and postoperative
386 activity, might explain the rest of the variance in the Δ medial ratio. Our results
387 demonstrated that HKA, but not age and BMI, was significantly correlated with the

388 medial ratio in both healthy individuals and patients with OA, and that only Δ HKA was
389 significantly correlated with the Δ medial ratio among variances (age, sex, BMI, JOA knee
390 score, and pre-, postoperative and Δ values of HKA and PTS). In addition, a 3-D motion
391 analysis study demonstrated that among the changes in the mechanical axis angle, PTS,
392 gait speed, and lateral trunk lean, only the change in the mechanical axis angle was
393 significantly correlated with the change in KAM during level walking before and after
394 HTO.²⁸ Thus we can conclude that leg alignment is an important factor influencing the
395 stress distribution pattern across the proximal tibial articular surface.

396 The comparison between the patients postoperatively and the controls revealed
397 that although the patients had valgus alignment more than did controls, the medial ratio
398 was still higher in the patients postoperatively. A possible explanation for this dissociation
399 between the alignment and the medial ratio is the influence of OA itself on the
400 subchondral bone density.^{19, 39} Another possible explanation is that the distribution of
401 bone density 1.5 years after HTO was not the final distribution of bone density after HTO,
402 inasmuch as the DEXA study mentioned earlier demonstrated that a medial-to-lateral
403 ratio of femoral and tibial condyle BMD was still changing 1 year after HTO.²⁵ Further
404 study is needed to clarify when the final distribution of subchondral bone density is
405 established.

406 The results of our subregional analysis of HDA distribution pattern before and
407 after HTO demonstrated that, of the four subregions in the medial compartment, %HDA
408 of M2 and M3 decreased after HTO, whereas M4 was the only region of the medial
409 compartment to exhibit increased %HDA. These results suggested that stress on the most
410 lateral region of the medial compartment increases after HTO. A finite element study has
411 reported that shear stress on the lateral region in the medial compartment increases as
412 lateral joint line obliquity increasing.³⁶ This might be a reason for the paradoxical
413 observation that the stress increases on the most lateral region only but decreases for all
414 other regions. Further study is required to clarify whether this effect influences long-term
415 clinical outcomes; however, surgeons should consider the risk of progression of OA at the
416 most lateral region of the medial compartment after HTO due to increased mechanical
417 stress, especially in cases where changes in OA have occurred in this region. In this study,
418 the mean medial ratio was higher in the OA (80.1%) than control group (61.3%), which
419 is consistent with a previous biomechanical study in which the percentage of total loading
420 attributable to medial compartment loading was 66% in the control group (with normal
421 alignment) compared with 74.5% in patients with OA at the first peak of the KAM.²⁶ The
422 similarity between the medial ratio of this study and the medial compartment loading ratio
423 in the previous study²⁶ provides some support and verification of the reliability of CT–

424 osteoabsorptiometry as a method for evaluating stress distribution.^{12, 17, 18, 31, 32, 34, 37, 41, 46}

425 There are different opinions about the leg alignment after HTO. Some authors
426 recommend HKA of 3°–5° valgus,^{13, 14} others suggest 8°–10° valgus.^{9, 24} Fujisawa et al.
427 suggests %MA of 65%–70%.¹¹ However, the medial compartment loading correlated with
428 the tibiofemoral alignment in the dynamic single-limb loading ($R^2 = 0.59$) with varus
429 malalignment,²⁷ indicating that same leg alignment does not indicate the same distribution
430 pattern of the joint loading. Therefore, it is thought to be desirable that the postoperative
431 leg alignment of each patient is decided considering the distribution of the joint loading.
432 Further investigation including of the distribution pattern of subchondral bone density
433 and kinematic analysis including KAM can be useful for elucidating the optimal leg
434 alignment of each patient who underwent HTO.

435 This study has several limitations that should be acknowledged. First, we did not
436 directly measure the stresses and the overall bone density in the knee. Instead, the
437 distribution of subchondral bone density in the knee joint was assessed according to the
438 CT–osteoabsorptiometry method.^{31, 32} Furthermore, the absolute value of stress at each
439 analysis point was not elucidated. Therefore, it should be kept in mind that the stress
440 distribution evaluated by the CT–osteoabsorptiometry method does not reflect actual
441 stress at the analysis points. Second, there was a significant difference in age between the

442 OA and control groups (mean difference 38.1 years). This study reveals that age is
443 correlated with the medial ratio in patients with OA but not in healthy individuals.
444 However, leg alignment was found to be correlated with medial ratio in both groups. This
445 indicates that age might influence the distribution of subchondral bone density as strongly
446 as varus alignment. Third, we evaluated patients with OA after the removal of metal
447 component. Finite element analysis has been used to demonstrate the stress shielding
448 effect of the HTO plate on the bone around the plate²²; however, the mechanisms
449 underlying this effect on the articular surface are unclear. Moreover, regardless of the
450 stress shielding effect of the HTO plate, this study reveals that the distribution of
451 subchondral bone density differs significantly before and 1.5 years after HTO. A fourth
452 limitation was the small sample size. We included the patients who underwent OWHTO
453 and excluded those with meniscus injury, joint instability, patellofemoral OA, and lateral
454 OA. Our results may have consequently been affected by the inclusion of patients only
455 with good outcomes, especially in view of the small sample size. At our institution,
456 however, we perform closed HTO²³ for patients with severe varus OA ($HKA \leq -10^\circ$) or
457 patellofemoral OA (KL grade \geq II). In general, closed HTO necessitates fibular osteotomy,
458 which itself might affect stress distribution across the knee joint.⁴⁸ Each exclusion
459 criterion was believed to be a contraindication to HTO or a factor other than HTO that

460 affects the stress distribution. We thus believed that the inclusion and exclusion criteria
461 were necessary for this study to evaluate the influence of HTO alone on the distribution
462 of subchondral bone density as accurately as possible. Despite these limitations, the
463 results presented here provide fundamental clarification of the stress distribution over the
464 knee joint.

465 In conclusion, we demonstrated that the distribution pattern of the HDA shifted
466 from the medial-to-lateral compartment after HTO. We discovered that leg alignment was
467 correlated with the distribution of subchondral bone density among nonarthritic
468 individuals and patients with OA, and that the degree of alignment correction after HTO
469 was correlated with the change in the distribution of the HDA. Moreover, we found that
470 the HDA of the most lateral region in the medial compartment decreased after HTO.

471 These findings suggest that HTO reduces the stress on the medial compartment
472 of the proximal tibial articular surface in knees with varus OA by shifting the stress toward
473 the lateral compartment, and that the stress on the most lateral region of the medial
474 compartment increases after HTO, inasmuch as the change in subchondral bone density
475 results from the change in stress distribution.

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